Geographical variation in dementia

Geographical variation in dementia: systematic review with meta-analysis

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Key messages: Identifying geographical variation in dementia prevalence and incidence could lead to the identification of potentially modifiable risk—or protective—factors. This review identifies evidence, based on within-study comparisons, at a variety of scales of geographical variation of dementia. Furthermore, there is evidence from meta-analysis of an association between rural living and AD, particularly for early life rural living.

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SUMMARY

Background: Geographical variation in dementia prevalence and incidence may indicate important socio-environmental contributions to dementia aetiology. However previous comparisons have been hampered by combining studies with different methodologies. This review systematically collates and synthesises studies examining geographical variation in the prevalence and incidence of dementia based on comparisons of studies using identical methodologies.

Methods: Papers were identified by a comprehensive electronic search of relevant databases, scrutinising the reference sections of identified publications, contacting experts in the field and re-examining papers already known to us. Identified articles were independently reviewed against inclusion/exclusion criteria and considered according to geographical scale. Rural/urban comparisons were meta-analysed.

Results: Twelve thousand, five hundred and eighty records were reviewed and fifty eight articles were included. Dementia prevalence and incidence varies at a number of scales from the national down to small areas, including some evidence of an effect of rural living (prevalence OR 1.11, 90% CI 0.80, 1.53; incidence OR 1.20, 90% CI 0.84, 1.71). However this association of rurality was stronger for Alzheimer disease, particularly when early life rural living was captured (prevalence OR 2.22, 90% CI 1.19, 4.16; incidence OR 1.64, 90% CI 1.08, 2.50).

Conclusions: There is evidence of geographic variation in rates of dementia in affluent countries at a variety of geographical scales. Rural living is associated with an increased risk of Alzheimer disease and there is a suggestion that early-life rural living further increases this risk. However few studies in resource-poor countries limits conclusions.

MeSH Keywords : Dementia; Alzheimer disease; Epidemiology; Geography; Disease Clustering

INTRODUCTION

Tobler's first law of geography states that the relationship between entities is stronger when they are close than when they are distant.[1] In epidemiology, this is equally true for disease occurrence: clustered areas of low or high incidence may implicate environmental exposures associated with the disease and this may have important public health consequences. Leukaemia demonstrates geographical clustering that may be related to proximity to nuclear facilities.[2, 3] Similarly the worldwide variation in multiple sclerosis rates suggests a complex interplay of genetic and environmental factors such as climate, diet, geomagnetism, toxins and infection.[4-6] Clustering in both space[7, 8] and space-time[9] in schizophrenia has been described. While systematic reviews of geographical variation in dementia exist,[10-12] previous aggregations of the evidence have relied on the *ad hoc* comparison of dementia occurrence across studies focusing on contrasting geographic locations (e.g., different countries or urban and rural areas).

However data from a single study in one geographical location cannot be directly compared with another single centre study from another location because methodological differences between the studies, for example differing diagnostic criteria or the way they are operationalised, may produce artefactual differences in prevalence or incidence. Accordingly, we provide an update of this evidence together with meta-analysis examining geographical variation in the prevalence and incidence of dementia from within-study comparisons.

METHOD

Information sources

We adopted a four-pronged approach to identifying relevant studies. First, we conducted an electronic search of relevant databases. Second, we scrutinised the reference sections of identified publications. Third, we contacted experts in the field. Fourth, we re-examined papers already known to us. Searches were conducted by an Information Scientist (CF). Table 1 shows

databases utilised, with dates. Comprehensive search criteria were developed iteratively. The full electronic search strategies for all databases used, including limits applied, are reported in the appendix. Results of the literature search were independently screened in parallel by two reviewers (TR and GH). Abstracts of relevant titles were reviewed and the full text of each highlighted article was obtained.

Eligibility criteria

Inclusion criteria were: cross-sectional and longitudinal studies of any length offering a comparison of dementia prevalence or incidence between two or more different sites, at any geographical scale. Grey literature and theses were included. We did not limit the search by language (as long as there was an English language abstract) with the intention of having relevant papers translated. We also included papers in languages other than English if other reports from the same study had been published in English to allow adequate assessment of the methodology and this further report contained relevant data. Papers could consider all causes of dementia apart from those secondary to external causes or where dementia is a later, secondary feature of the disorder, e.g. alcohol or traumatic brain injury, Parkinson's disease, Huntington's disease and Creutzfeld Jakob Disease, either sporadic or variant.

Exclusion criteria were: papers comparing studies using external comparison groups, which were conducted independently or which used different methodologies (for example, the EURODEM/EuroCoDe papers[13-16] or other 'quantitative integrations of the literature'[10]); studies with no spatial variable—e.g. comparing different ethnic groups or investigating aluminium or silicate concentrations in water; and references with no abstract and a vague title (e.g. 'epidemiology of dementia'). Studies focussing purely on young onset dementia were excluded in order to reduce heterogeneity in the review.

A large number of papers describe the clusters of amyotrophic lateral sclerosis/parkinsonism-dementia complex in the Pacific basin. This cluster was included since the condition is prominently characterised by dementia. Due to the wealth of literature describing these isolated clusters a representative paper was selected for inclusion.

Data collection

The principal summary measure was the prevalence or incidence of dementia in the two (or more) areas studied. Other data collected were the scale of comparison or areas which were compared, methods (including diagnostic criteria) and measures used, details and number of participants, including ages. The studies were also assessed for quality of design and methodology from A (best) to E (worst), including a consideration of bias. This measure of quality took into account quality and limitations of case-finding procedures, diagnostic criteria used, standardisation across sites and completeness of follow up in longitudinal studies.
Estimates of error were not reported by all authors, limiting the precision of comparisons of reported prevalence or incidence rates. Where possible, reported *p* values were converted to 95% confidence intervals (CI).[17]

Meta-analysis

Numbers of cases and non-cases in studies comparing prevalence or incidence of dementia in rural and urban areas were used to compute odds ratios (OR) with accompanying 90% CIs, in line with statistical guidance.[18] Urban areas formed the referent in all models. Where raw numbers were not reported, odds ratios and 95% CIs were converted to log odds ratios and log variances. These study-specific estimates of prevalence and incidence were meta-analysed, using random-effects models since there was a large amount of heterogeneity (prevalence studies: I^2 89.5%; incidence studies: I^2 81.2%). Authors of studies reporting insufficient data[19-21] were contacted, apart from Leighton et al.[22] for whom contact details were unavailable.

Sensitivity analyses

One prevalence study classified participants according to more than one set of diagnostic criteria.[23] In the main analyses, the results using DSM-IV criteria were used. We also examined the effect of altering the diagnostic criteria used and the effect of excluding the study completely from the models. We conducted a further sensitivity analysis stratifying the prevalence and incidence meta-analyses by study quality.

Statistical analyses were conducted using R version 2.15.0[24] and the metafor package.[25] Figures 3 and 4 were drawn with the R package Rmeta.[26] The reporting of this systematic review conforms to the PRISMA statement.[27]

RESULTS

A total of twelve thousand, five hundred and eighty records were screened and the two reviewers (TR & GH) produced shortlists of one hundred and sixty four and one hundred and seventy three papers, respectively, that potentially matched inclusion criteria. Of these one hundred and twelve studies were excluded (reasons for exclusion are outlined in Figure 1 which shows the screening process) leaving fifty two articles (from thirty five unique studies) which are summarised in Tables 2-6.

The studies included were conducted across the world, though predominantly in high-income countries (Europe, Canada and the USA). The studies ranged in size from three hundred and twenty one[28] to the entire population of the USA.[29] Methodologies included multiple-phase population surveys (n=23[19, 21, 30-50]), one-phase surveys (n=12[22, 23, 28, 51-59]), using death certificate data (n=9[20, 29, 49, 60-65]), and case registers (n=8[66-72]). Twelve studies included a longitudinal design allowing dementia incidence to be ascertained.[19, 31, 33-35, 38-41, 43, 58, 59]

Diagnostic criteria used included the International Classification of Diseases (ICD), ninth revision[73] (n=7[20, 53, 59, 63, 68-70]) or ICD-10[74] (n=11[35-37, 42, 43, 46, 47, 50, 60, 62, 65]), the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III[75] or DSM-III-R[76]; n=13[32-36, 39, 42-45, 48, 49, 52]) or DSM-IV[77] (n=7[19, 23, 46, 47, 50, 57, 58]). Twelve studies did not state the diagnostic criteria they used.[21, 22, 30, 31, 33, 34, 38-41, 61, 64] Tests used included the Mini Mental-State Examination[78] (MMSE) in various languages (n studies=9[19, 21, 30, 31, 37, 38, 40, 41, 46, 47, 49-51]), the modified MMSE[79, 80] (3MS; n=4,[32-34, 39] all part of the Canadian Study of Health & Aging), the Community Screening Instrument for Dementia[81] (CSID; n=4[35, 36, 42, 43], all part of the Ibadan-Indianapolis study), the cognitive part of the Cambridge Examination for Mental Disorders of the Elderly [82] (CAMCOG; n=4[31, 40, 41, 50]), the Comprehensive Assessment and Referral Evaluation (Care) or short-Care interview[83] (n=2[28, 54]) and the Mental Status Questionnaire[84] (MSQ) or Short Portable MSQ[85] (n=2[28, 59]). Three studies[31, 40, 41, 52, 55, 56] used the Geriatric Mental Schedule (GMS) and the Automated Geriatric Examination for Computer Assisted Taxonomy[86, 87] (AGECAT). Twenty-three studies included a clinical assessment of participants.[19, 21, 30, 32-39, 42-49, 58, 66, 67, 71]

The papers included in the review were divided into groups reflecting the scale of comparison. Each group will be considered in turn, comparing rates between countries or nationwide surveys, rural and urban areas, regions, towns or cities and smaller areas.

Country-by-country comparisons or nationwide surveys

Table 2 summarises the results of studies identified which compared rates of dementia between countries. There were two main methodologies used at this scale: comparing mortality rates (of the whole population or a sample) between two or more countries, and identifying the country of birth of individuals in a discrete area in a single country.

Age-adjusted Alzheimer disease (AD) mortality in 1999 was reported as 15.9% in the USA compared to 21.2% in Puerto Rico.[60] Rates for 2004 were 20.9% and 32.4%, respectively. They conjectured that the increase in dementia rates might be explained by improved survival.

The "Colombo 2000" project found disease-specific mortality rates for AD to be higher in Italy (9.8/10 000) than in Argentina, which has a large Italian immigrant population (3.4/10 000).[64, 88] Another study comparing random samples of the over-60s found that the proportion scoring less than twenty out of thirty on the MMSE was 4.5% in Argentina, 9.4% in Chile and 7.2% in Cuba.[51] With a higher cut-off of twenty two or less out of thirty, the proportions were Argentina 4.5%, Chile 19.7% and Cuba 16%.

The 10/66 Dementia Research Group focuses particularly on the under-researched (and therefore resource-poor) areas of the world.[23, 57] The authors found a much lower prevalence of dementia by DSM-IV than by 10/66 consensus criteria in India (rural and urban) and Peru (rural only) (Figure 2). Dementia prevalence was found to vary between countries, although the directly-standardised prevalence rates differed with the diagnostic criteria used: compared to other sites prevalence of dementia was higher in Cuba (10/66 criteria: 12.6%, 95% CI 10.4-14.9; DSM-IV: 6.3%, 95% CI 5.0, 7.7) and the Dominican Republic (10/66: 9.8%, 95% CI 8.1-11.1; DSM-IV: 4.2%, 95% CI 3.3, 5.1) and lower in rural China (10/66: 4.8%, 95% CI 3.1, 6.4), rural Peru (DSM-IV: 0.4%, 95% CI 0.0, 1.0) and both rural (DSM-IV: 0.3%, 95% CI 0.1, 0.5) and urban India (DSM-IV: 0.9%, 95% CI 0.3, 1.6).

The remaining studies used the second methodology mentioned above—identifying the country of birth of individuals in a single area, thus providing insight into the effect of place of birth on the risk of developing dementia. The Islington study interviewed house-to-house and grouped the over-65s by country of birth.[54] They found no relation between migration *per se* and dementia.

However the relative risk for developing dementia did vary by place of birth, being lower in the Irish population (RR 0.36, 95% CI 0.15, 0.87) and higher in the case of people born in Africa or the Caribbean (RR 1.72, 95% CI 1.06, 2.81) when compared to British-born residents. Another London-based study found a higher dementia prevalence in African-Caribbean-born residents of Haringey compared to the White UK-born population (OR=3.07, 95% CI 1.28–7.32).[50]

Rural/Urban comparisons

Table 3 outlines publications comparing rates of dementia in rural and urban areas. The rural/urban comparisons were quantitatively examined by meta-analysis where possible with the remaining studies being summarised narratively.

Papers which reported (or provided) sufficient prevalence[21, 23, 30, 37, 40, 42, 47, 49, 67] or incidence[19, 34, 40, 43] data were meta-analysed using random-effects models and results are shown in Figures 3 and 4 respectively. Urban areas form the reference group throughout. Out of the authors contacted, two replied providing data for inclusion in the meta-analysis.[19, 21] Two articles were excluded due to reporting insufficient data.[20, 22] The latest report from the 10/66 Dementia Research Group was excluded because it did not give sufficient data for inclusion despite reporting a slightly later stage of the study.[57]

There was evidence of an association between rurality and prevalence of AD[37, 42, 47, 67] (OR 1.50, 90% CI 1.33, 1.69) and vascular dementia[37, 47] (OR 1.33, 90% CI 1.10, 1.62). Evidence was weaker for an association between rurality and non-specific dementia prevalence[21, 23, 30, 37, 40, 49] (OR 0.91, 90% CI 0.58, 1.41). Pooling all prevalence studies regardless of diagnostic subtype[21, 23, 30, 37, 40, 42, 47, 49, 67] resulted in an intermediate risk of dementia (OR 1.11, 90% CI 0.80, 1.53).

Only one prevalence study classified participants according to more than one set of diagnostic criteria.[23] Altering the criteria used had a substantial effect on the association between non-specific dementia and rurality: using DSM-IV criteria OR 0.91 (90% CI 0.58, 1.41); using 10/66 consensus criteria OR 1.13 (90% CI 0.81, 1.56); and excluding the four comparisons reported in this study: OR 1.39 (90% CI 0.75, 2.23). Combining all prevalence studies regardless of diagnostic subtype showed a similar pattern: DSM-IV OR 1.11 (90% CI 0.80, 1.53); 10/66 OR 1.25 (90% CI 0.97, 1.61); and excluding the study OR 1.44 (90% CI 1.03, 2.01).

Stratifying prevalence studies by quality reduced the association between rurality and dementia (Studies rated D or better:[21, 23, 37, 40, 42, 47, 49, 67] OR 1.15, 90% CI 1.02, 1.71; C or better:[23, 37, 40, 42, 47, 49, 67] OR 1.03, 90% CI 0.80, 1.32; B or better:[23, 37, 40, 42, 47] OR 0.95, 90% CI 0.69, 1.29) apart from the two comparisons from the one study rated A for quality[42] which captured early life rural living in which there was an increased association between rurality and AD (OR 2.22, 90% CI 1.19, 4.16).

There was evidence of an association between rurality and dementia incidence[19, 34, 40, 43] (OR 1.20, 90% CI 0.84, 1.71), stronger for AD[43] (OR 1.64, 1.08, 2.50) than for non-specific dementia[19, 34, 40] (OR 1.01, 90% CI 0.64, 1.60). Restricting the meta-analysis to incidence studies rated A for quality[19, 43] (no incidence study was rated lower than B) had little effect on the association with rurality (OR 1.17, 90% CI 0.66, 2.06).

[19, 43] There was no evidence of publication bias on formal testing (regression test for funnel plot asymmetry: prevalence studies $z = -1.35$, $p = 0.18$; incidence studies $z = 1.51$, $p = 0.13$).

Among the studies reporting insufficient data for meta-analysis a study examining all Japanese death certificates from 1979-1990 found that the AD mortality was similar for rural and urban

areas[20] and a study in Nigeria found that prevalence of 'chronic brain syndrome' did not vary between Yoruba villages and a nearby town in men (6%) but did in women (5% vs 9%).[22]

Regional comparisons

'Region' here refers to an area within a country larger than a town or city. Table 4 summarises the results of studies identified which compared rates of dementia between regions.

The Canadian Study of Health & Aging reported a similar prevalence of dementia across Canada but suggested that the relative prevalence of dementia subtypes varied across regions.[32-34] Particularly low prevalence of dementia in Ontario males was explained by discrepancies in the use of diagnostic criteria.[32] Another Canadian study concluded that dementia prevalence varies little across regions.[39] They did note differences between community and institutional samples and noted that dementia prevalence was higher in areas of lower socio-economic status. In rural Manitoba, Canada, the prevalence of dementia among the Cree was found to be the same as a non-Native sample in Winnipeg but there was just one case of AD identified in the Cree (0.5%) compared to 20 in the Winnipeg sample (8.3%; age-adjusted rate 3.5%, 95% CI 2.1, 4.8; $p < 0.001$).[48]

A comparison of all dementia deaths in 1999/2000 and 2005/6 across the USA at the county level showed a pattern of marked variation in dementia and AD mortality different to that of cardiovascular disease and stroke.[65] Three "co-operative longitudinal studies" in the USA reported 6-year incidence rates of 29.8% in East Boston, 25.0% in New Haven and 20.4% in Iowa.[59] Using stricter criteria reduced the variation between sites (East Boston 15.4%, New Haven 14.3%, Iowa 11.3%). Prevalence of AD in South Carolina showed "notable variation" at a county level.[68-70] However, it was unclear whether the location was where the individual was born or where they were lived as an adult. Clustering of AD deaths in the north-west and south-east of

the USA with a four-fold difference in rates between the highest and lowest was identified over the period 1999-2004.[29] A study in Puerto Rico noted variation in mortality rates with dementia in the eight regions of the island.[60]

The amyotrophic lateral sclerosis/parkinsonism-dementia complex clusters in the Chamorro population of Guam (one of the Mariana Islands in the western Pacific Ocean) and elsewhere have been extensively studied.[89] A representative study on Guam identified an incidence gradient, with higher prevalence in southern and central Guam and lower prevalence in northern and western Guam.[72, 90] More recent reports have not focussed directly on the geographical spread of cases.[91] There have been suggestions that this cluster could be related to the consumption of a palm, *Cycas micronesica*, but this has not been definitively proven.[92] Similar clusters have been described on the Kii peninsula of Japan—with prevalence in two villages approximately one hundred times that in the rest of the country[93]—and in West New Guinea.[94]

An examination of Australian death certificates revealed a much higher prevalence of dementia at death in Tasmania and 'senility' in South Australia than the rest of the country. [63] Dementia prevalence at death was predominantly related to place of death but those who were born and died in Tasmania had the highest rate of all. In Tasmania, 43% of dementia death certificates were linked to a single practitioner.

A Japanese study found that AD mortality varied across the country with Miyazaki prefecture approximately double and Okinawa approximately half the overall national rate.[20] Across four areas of China, a north-south gradient in dementia prevalence, particularly for vascular dementia, and a less pronounced east-west gradient were identified.[46, 47]

The MRC Cognitive Function and Ageing study concluded that there was no evidence of variation in incidence or prevalence of dementia in England and Wales.[31, 40, 41] The incidence of dementia in a working class, urban area of Spain was double that in both the agricultural and professional class urban areas.[19] A Finnish study found a higher prevalence of AD in the north and east of the country than elsewhere.[44, 45]

Town/City comparisons

Table 5 outlines the papers comparing rates of dementia between towns and cities.

The Ibadan-Indianapolis study identified a higher age-adjusted prevalence of dementia in Indianapolis, USA (4.82%) compared to Ibadan, Nigeria (2.29%; AD 3.69% vs 1.41%).[36, 42]At follow-up, age-standardised annual dementia incidence rates were higher in Indianapolis (3.24%, 95% CI 2.11, 4.38; Ibadan 1.35%, 95% CI 1.13, 1.56), as were age-standardised annual AD incidence rates (Indianapolis 2.52%, 95% CI 1.40, 3.64; Ibadan 1.15%, 95% CI 0.96, 1.35).[35, 43]

The rates of dementia in the institutionalised elderly with moderate or severe dementia in New York and London were found to be similar.[28] A later study found that rates of organic illness were higher in New York for both men (5.7%; London 2.2%) and women (10.1%; London 5.4%).[52]

In Okinawa, there was some evidence of variation in rates of dementia between Sashiki village and Ikema island but these were not formally compared and used an idiosyncratic case classification.[53]

No difference in dementia prevalence was found between Zaragoza, Spain and Liverpool.[55, 56] Furthermore they identified no sex or age differences. The 3C study found no differences in the distribution of cognitive test scores in three cities across France.[58]

Small area comparisons

Large-scale (or small area) comparisons are potentially the most informative with regard to identifying socio-environmental risk factors for dementia. Table 6 outlines the papers making such comparisons.

Death certificates for the over-70s were examined in Newfoundland, Canada and two areas had substantially higher dementia mortality rates.[61] An excess of individuals born on the north shore of Bonavista Bay dying with dementia was identified (14.3%; south shore 2.9%). This was not related to differential survival or sex-distribution but may have been affected by kinship and migration. Projet IMAGE found no real variation in standardized prevalence rates of dementia in an area of Québec, Canada, despite a trend in two areas.[66, 67, 71] A Swiss study identified a dose-response relationship between the length of time living within 50m of a power line and developing AD. [62]

DISCUSSION

Main findings

All published studies indicate that the prevalence and, in one case, incidence of dementia varied between countries but the precision of estimates was not always clear. Comparing rural and urban areas, there was evidence for an association between rurality and prevalence and incidence of AD and prevalence of vascular dementia. The association with AD prevalence was increased in studies which captured early life rural living. There was less evidence for an association with prevalence or incidence of a general category of dementia. At a regional level, the findings were

mixed with some,[31-34, 40, 41] but not all,[19] of the better quality studies suggesting that there is little evidence of variation in dementia prevalence or incidence. However very few studies report data supporting their findings, limiting the certainty of conclusions.

There were fewer studies at larger scales and so conclusions must be tentative. However, the best quality studies did find variation in dementia incidence between towns/cities.[35, 36, 42, 43] The 3C study[58] did not but reported the distribution of cognitive test scores rather than actual diagnoses of dementia. At the most informative (i.e. smallest) scale, there were fewest studies. However all except for Projet IMAGE[66, 67, 71] found evidence of variation in dementia prevalence. There were no studies of dementia incidence at this scale.

To summarise, there is evidence, at all scales, of geographical variation in the prevalence or incidence of dementia and, specifically, a higher risk of AD and vascular dementia in rural areas. At first glance, the different patterns seen at different scales seem contradictory and confusing. However this is a common finding with geographical data, the *modifiable areal unit problem* where, "if the spatial units in a particular study were specified differently, we might observe very different patterns and relationships."[95] Unfortunately none of the included studies collected their data or conducted their analyses at more than one scale, which might shed some light on this ubiquitous problem of spatial data.

The definition of rurality

There was substantial heterogeneity in the studies comparing rural and urban areas. This is likely to be due, at least in part, to the notoriously difficult definition of 'rurality.' A Japanese study defined an administrative unit as 'rural' if the population numbered thirty thousand or fewer.[20] In Sicily, the isolation of rural Troina (where the "economy is almost completely based on farming and grazing.") is contrasted with the urban area "connected by rail, sea, a regional road, and a

motorway… [where] the economy is more diversified.".[30] The 10/66 Dementia Research Group defined rural areas "by low population density, and traditional agrarian lifestyle."[96] Projet IMAGE defined a rural area as containing villages rather than cities.[97, 98] Nevertheless it is surprising how many studies do not explicitly define rurality—for example neither Liu et al[38] nor investigators in the Canadian Study of Health & Aging [32, 34, 99] provided a definition of rurality. This is easier to understand when comparing extremes, for example a large city and distant villages, when the difference is obvious. However, it becomes more difficult to make subtle distinctions. Indeed a perfect definition may remain elusive and the epidemiological importance may not lie in the contrast but, rather, in the optimum population density (as has been demonstrated for cardiovascular disease and stroke in men[100]) and access to health services and factors conducive to a healthy lifestyle.

Young-onset dementia

While studies purely examining young-onset dementia were excluded from this review, there are a number of relevant studies which echo the findings in late-onset dementia. A study in Israel—using country of birth as the spatial variable—found age- and sex-adjusted incidence rates for European-American-born individuals to be double that of African-Asian-born people.[101] At a larger scale, a study in Edinburgh identified all 55 unrelated cases of young-onset AD admitted to hospital and noted high prevalence in two geographical areas.[102] A subsequent study of young-onset dementia across the whole of Scotland looked at the geographical distribution of cases and found non-random distribution of cases of young-onset AD but not vascular dementia.[103-106] This pattern was partly, but not entirely, explained by kinship, suggesting that socio-environmental factors may also play a role in the aetiology of young-onset dementia.[104]

Limitations of the review and risk of bias within and across studies

The methodology of this review was systematic and robust and the wide, professionally-conducted search and two independent reviewers are likely to have identified all the available literature.

There is the possibility that variation in dementia prevalence or incidence might be the result of chance but this review includes a large number of studies, many of them methodologically robust, which have found variation, suggesting that chance is unlikely to be behind all of them. Furthermore all the studies included in the review offer within-study comparisons minimising the possibility that identified variations in prevalence or incidence are the result of methodological differences between studies.

The first and most profound limitation to and source of bias in this review is the lack of attention paid to epidemiological studies of dementia in large areas of the world,[107] a point noted and beginning to be remedied by bodies such as the 10/66 Dementia Research Group,[23, 57] but also highlighted recently in relation to studies in Eastern and Middle European Countries.[16] This is particularly important since it is predicted that increases in dementia prevalence will be larger in the developing world than elsewhere.[107, 108] Until there are good quality epidemiological studies across the world, no conclusions regarding the global variation of dementia can be any less than conjectural.

There are significant methodological difficulties involved when comparing epidemiological studies, such as the method and thoroughness of case-finding,[10] whether the entire population or a sample will be studied[109] and the choice of study setting itself. These difficulties are compounded in studies of dementia by consideration of different diagnostic criteria and whether or not to include mild cases,[10] let alone individuals with 'mild cognitive impairment.' Further

biases such as differential survival and consequent differing age structures of populations, variation in diagnosis rates and reporting of dementia,[63, 110] screening non-participation and validation,[111] access to health care and levels of health and education make conducting and interpreting such studies—even when they are methodologically identical—extremely difficult.[11] These challenges are likely to have produced some bias in the studies and are reflected in the variation in quality ratings for the studies. One interesting finding from two studies[51, 59] is that geographical variation reduces with stricter diagnostic criteria confirming Jorm's assertion that the inclusion or exclusion of milder cases can have an important effect on the findings of quantitative studies of dementia.[10]

Thinking further about diagnostic criteria, no studies investigated definitive neuropathological diagnoses and so differential rates of dementia sub-types must be considered no more certain than 'probable,' in line with diagnostic criteria.[112-116] Therefore the possibility remains that the clinical diagnoses reported in these studies may not perfectly reflect neuropathology, as has been shown previously.[117, 118] The common neuropathological finding of mixed pathologies further complicates matters. This suggests that conclusions regarding specific dementia subtypes should be considered tentative.

A large number of studies rely on case registers or death certificate data. These methodologies are highly susceptible to bias in that the diagnosis has to be correctly made, recorded and transcribed into the appropriate record. Estimated rates of accurate dementia reporting on death certificates are 25-58%[110, 119] but more recent studies suggest that this is improving, for example in a cohort of 502 deceased individuals with probable AD 359 (71.5%) had dementia correctly recorded as a cause of death.[120] Furthermore there is a potential spatial confounder in that clinical service provision or quality may vary with geography, resulting in variation of dementia prevalence as in

one study where 43% cases in a cluster could be linked back to just one clinician, who presumably had a particular interest in dementia.[63]

More robust are screening studies, particularly two-stage screening designs and especially when the whole population is screened rather than a sample. However, there is still danger of selection bias creeping in.[111] The best quality studies included were the Neurologic Disorders in Central Spain study[19] and, despite numerous methodological challenges—including estimating the ages of some of the Yoruba interviewed—the Ibadan-Indianapolis study.[35, 36, 42, 43] Both studies showed variation in dementia incidence and the latter showed variation in AD prevalence.

The cultural validity of tests and rating scales, even if translated, is often unclear. Furthermore, cultural factors related to ageing and functional decline are also highly relevant to variation and a source of bias. Different cultures react to and accommodate ageing in different ways and will treat symptoms of cognitive and functional decline differently. We must not ignore the implicit value-laden nature of many, if not all, diagnoses,[121] even dementia—for example what level of functioning can be expected at what age—and the variation of these values in different countries and different cultures. In fact, from a global perspective, the individual with dementia may not be a fixed kind of person but what Hacking describes as a "moving target."[122]

Further potential confounders include differential survival or migration—for example, if individuals at highest risk of developing dementia in an area die or move away, those remaining will have an artefactually low prevalence of dementia. Both migration[61] and differential survival[35, 36, 42, 43, 61] were considered by a small number of the studies. The methodology most susceptible to bias by migration is comparing country of birth of individuals living in a discrete geographical area. That the finding that risk of dementia is increased in people born in Africa or the Caribbean[50, 54] is not matched by increased rates of dementia in these countries suggests that

migration may have confounded the studies using this methodology. Similarly genetic relatedness is a factor which must be taken into account and was estimated by some of the studies included.[61, 103, 104, 123]

The spatial variable must also be recorded for a sufficiently early point in life to avoid reverse causality, for example mapping the location of death of people with dementia may merely identify the locations of care homes or hospitals with long-stay beds.[110]

The relative dearth of larger-scale comparisons—for example regions, towns or postal districts—limits the precise assessment of any variation which might be found and thus the conclusions which can be drawn about possible socio-environmental exposures.

This review explicitly excluded papers comparing studies conducted independently or with different methodologies. Therefore there are potentially further studies looking, for example, at rates of dementia in rural areas, but the methodological difficulties in combining these with separate studies preclude such a comparison. This criterion is unlikely to have introduced substantial bias but clearly reduces the data available substantially with a consequent impact on confidence intervals for effect estimates.

Implications

Apart from implications for health service provision, the real interest in identifying variation in the prevalence and incidence of a disease is in identifying potentially modifiable risk factors. Many socio-environmental risk factors are likely to have their effect on dementia risk early in life,[124-126] though not all studies confirm this association.[127] Some of studies included in the current review examined early life effects, for example place of birth[61] or living in a rural area in childhood,[42, 43] but the majority measured their exposures at the time of the study. The

rural/urban meta-analysis suggested that, while rural living may be associated with increased rates of AD, early life rural living may have an even greater effect. There are two possible implications of this finding—that exposure in early life has a greater effect or that duration of exposure determines the risk. Further research is required to clarify this finding.

However any consideration of geographical variation of dementia must also include geographical variation of related conditions and risk factors. Cardiovascular and cerebrovascular disease has been shown to vary in incidence across Scotland and this variation is partly related to smoking (in both sexes) and populations density, deprivation, blood pressure and body mass index (in men).[100] Temporal trends are also important. The possibility that changes in dementia incidence over time, and some geographical variation, might be related to improved survival following stroke has been raised.[128, 129] Detailed examination of secular trends in dementia, related conditions, and risk factors is required.[130]

Given the early effects of some risk-factors and the presence of pathological changes of AD decades before the clinical onset of dementia,[131] any attempts at prevention will need to begin sufficiently early in life. A number of systematic reviews have shown that modifying risk factors in late life, for example lowering blood pressure[132] or treatment with statins,[133] are ineffective in preventing dementia, consistent with the evidence that many risk factors for dementia have their effects in mid-life or earlier.[134-137]

This need for sufficiently early intervention is reflected in the ideal methodology of dementia epidemiology studies and the importance of measuring risk factors—including location—at the most appropriate time point. Identification of any putative risk factors, at any geographical scale, requires their measurement to be at a sufficiently early stage for the findings to be clinically meaningful.

Conclusions

Though the extant evidence is far from consistent and varies in quality, prevalence and incidence of dementia does vary, at a number of scales: between countries, regions, towns and cities, and small areas. There is weak evidence for variation in dementia incidence or prevalence between rural and urban areas but stronger evidence for AD and vascular dementia. Furthermore, early exposure to rural living may have an increased effect on the association between rurality and AD.

Further work to provide higher quality evidence of geographical and temporal variation is required and comparisons could usefully be made with the geographical distributions of related conditions, such as stroke and cardiovascular disease. The next question is whether the causes of this observed variation can be identified and, if so, could they highlight modifiable socio-environmental risk factors thus making dementia a preventable disease?

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Table 1. Databases searched and dates of searches

Database	Database start	Date searched
ASSIA - Applied Social Science Index	1987	8/4/10
Embase	1974	8/4/10
FRANCIS	1984	8-9/4/10
GEOBASE	1980	8/4/10
Global Health	1973	9/4/10
Lilacs	1982	9/4/10
Medline	1950	8/4/10
PsycINFO	1806	8/4/10
CINAHL	1981	8/4/10
COPAC	1100	14/4/10
Scielo	1997	14/4/10
Ethos British Library these service	—	14/4/10
Australian Digital Theses Progam (ADT)	1998	14/4/10
Index to theses	—	14/4/10
ProQuest Dissertations and Theses	1861	15/4/10
Theses Canada Portal	1965	15/4/10
Conference Papers Index	—	15/4/10
PapersFirst	1993	15/4/10
ProceedingsFirst	1993	15/4/10

Table 2. Studies meeting inclusion criteria: Country-country comparisons or surveys comparing country of birth

Author	Year	Study	Setting	Methods	Measures	Diagnostic Criteria	Participants	Ages	Total N	Cases	Quality (A–E)
Anzola-Perez et al	1996	PAHO study [51]	Argentina, Chile & Cuba	One-phase survey	Spanish MMSE	MMSE score	Age- and sex-stratified random community samples	≥60	3 211	variable	D Methodologies differ slightly
Cristina et al Román	1997 1998	"COLOMBO 2000" project [64, 88]	Argentina & Italy	Death certificate data	—	Not stated	All AD deaths	Not defined	90.8 million	Not stated	E Relies on diagnosis being recorded; Population age-structures different
Livingston et al	2001	Islington Study [54]	Islington, London	One-phase survey	Short-CARE interview	Short-CARE	Random sample stratified by country of birth	≥65	1 085	107	C Good ascertainment; Use of place of birth confounds migration and other factors
Figueroa et al	2008	[60]	USA & Puerto Rico	Death certificate data	—	ICD-10	All AD deaths	Not defined	Census	Not stated	E Relies on diagnosis being recorded
Rodriguez et al Sousa et al	2008 2009	10/66 Dementia Research Group [23, 57]	Cuba, Dominican Republic, Peru, Venezuela, China & India	Cross-sectional comprehensive one-phase surveys	—	10/66 criteria DSM-IV	All residents in geographically-defined catchment areas	≥65	14 960	Not stated	B Screening difficulties possible; Standardisation between so many centres challenging
Adelman et al	2011	[50]	Haringey, London	Two-phase survey	MMSE CAMCOG	ICD-10 DSM-IV-TR Consensus criteria for sub-types	Random sample of GP lists stratified by recorded ethnic group/birth country	≥60	666	36	C Robust design but spatial variable is confounded by migration

Table 3. Studies meeting inclusion criteria: Rural/Urban comparisons (Articles in italic also appear in another table)

Author	Year	Study	Setting	Methods	Measures	Diagnostic Criteria	Participants	Ages	Total N	Cases	Quality (A–E)	
Leighton et al	1963	[22]	Nigeria: Yoruba villages and Abeokuta town	Population survey	—	not stated	People with 'chronic brain syndrome'	Not defined	326	~17	E	unclear
Imaizumi	*1992*	[20]	Japan	Death certificate data	—	ICD-9	All AD deaths	≥35	Total population	931	E	Relies on diagnosis being recorded
Emard et al *Perron et al* *Jean et al*	*1992* *1993* *1996*	Projet IMAGE [66, 67, 71]	Saguenay-Lac-Saint-Jean territory, Québec, Canada	Case register	Reisberg GDS Screening Clinical assessment	Adapted NINCDS-ADRDA	AD cases	Not defined	131 667 live births	235	C	Dependent on quality of case register; case ascertainment and representativeness of sample unclear; differential mortality a potential bias
Ebly et al *Manfreda* *Hébert et al*	*1994* *1995* *2000*	Canadian Study of Health & Aging [33, 34, 39]	All ten provinces of Canada	Two-phase screening Incidence study (5 years)	3MS Clinical assessment (including all institutionalised individuals)	Not stated	Random sample from community and institutionalised residents	≥65	6 449	97	B	Robust design but ascertainment unclear
Yip et al	1997	[49]	Taiwan: Ta-an district (urban) and Chin-shan Hsiang (rural)	Multi-phase survey	Chinese MMSE ADL scales Clinical assessment	DSM-III-R	Random sample of community stratified by age	≥65	1 733	29	C	Relatively robust but different response rates: 90 vs 71%
Liu et al Lin et al	1997 1998	[38] [37]	Southern Taiwan	Two-phase screening	Chinese MMSE Blessed DRS Clinical assessment	ICD-10-NA	Random sample stratified by rurality	≥65	2 915	108	B	Reasonable design
Azzimondi et al	1998	[30]	Sicily, Italy: Troina (isolated & rural) and S. Agata Militelo (a more developed small town)	Two-phase screening	Italian MMSE Clinical assessment	Not stated	50% random sample	≥75	773	196	E	No power calculation and no statistical comparisons; clinical assessment only of sample of borderline cases, not all who screened negative

Table 3 continues on the next page.

Table 3 continued

Author	Year	Study	Setting	Methods	Measures	Diagnostic Criteria	Participants	Ages	Total N	Cases		Quality (A–E)
MRC CFAS *Matthews et al* *Brayne et al*	*1998* *2005* *2006*	MRC CFAS [31, 40, 41]	UK: Four urban and two rural areas	Two-phase screening Incidence study (2 years)	GMS AGECAT MMSE GMS Assessmen CAMCOG	Not stated	Stratified random community sample	≥65	17 751 (prevalence) 7 175 (incidence)	630 incident	B	Robust design; unreported measures; two-fold variation in prevalence reasonable
Hendrie et al *Ogunniyi et al*	*1995* *2000*	Ibadan-Indianapolis Study [36, 42]	Ibadan, Nigerian and Indianapolis, USA	Two-phase screening	CSID Clinical assessment	DSM-IIIR and ICD-10	Community-dwelling Yoruba or sample of African Americans living in the community or in 6 representative nursing homes	≥65	5 117	165	A	Robust, identical methodologies
Hendrie et al *Ogunniyi et al*	*2001* *2006*	Ibadan-Indianapolis Study [35, 43]	Ibadan, Nigerian and Indianapolis, USA	Incidence study (2 and 5 years) Two-phase screening	CSID Clinical assessment	DSM-IIIR and ICD-10	Community-dwelling Yoruba or African Americans	≥65	4 606	187	A	Robust, identical methodologies
Zhang et al *Zhang et al*	*2005* *2006*	[46, 47]	Four regions of China	Two-phase screening	Chinese MMSE Clinical assessment Re-examination at 6 months	DSM-IV ICD-10	Stratified, multistage, cluster random sample from census	≥55	34 807	1 027	B	Thorough case-finding and 80-90% follow up; crude prevalences reported
Bermejo-Pareja et al	*2008*	Neurologic Disorders in Central Spain [19]	Spain: Las Margaritas, greater Madrid (working class), Lista, central Madrid (professional class) & Arévalo (agricultural)	Two-phase screening Incidence study (3 years)	Spanish MMSE Pfeffer activities questionnaire Clinical assessment	Consensus DSM-IV	Census data for geographically-defined areas	≥65	5 914 (prevalence) 3 891 (incidence)	306 prevalent 161 incident	A	Robust methodology
Rodriguez et al *Sousa et al*	*2008* *2009*	10/66 Dementia Research Group [23, 57]	Cuba, Dominican Republic, Peru, Venezuela, China & India	Cross-sectional comprehensive one-phase surveys	—	10/66 criteria DSM-IV	All residents in geographically-defined catchment areas	≥65	14 960	Not stated	B	Screening difficulties possible; Standardisation between so many centres challenging
Arslantaş et al	2009	[21]	Eskisehir city, Middle Anatolia, Turkey	Two-phase screening	Turkish MMSE Clinical assessment	Not stated	Random cluster sample of geographically-defined areas	≥55	3 100	262	D	Relatively robust methodology but 49.5% who failed MMSE declined further assessment and no one with MMSE >25 was assessed further

Table 4. Studies meeting inclusion criteria: Regional comparisons

Author	Year	Study	Setting	Methods	Measures	Diagnostic Criteria	Participants	Ages	Total N	Cases	Quality (A–E)
Sulkava et al Sulkava et al	1985 1988	Mini-Finland[44, 45]	Finland	Two-phase screening	Cattel's G-factor test Verbal memory test Clinical assessment	DSM-III	Representative sample of Finnish population	≥30 (≥75 for dementia project)	8 000	141	B Robust design and representative sample.
Jorm et al	1989	[63]	Six Australian states	Death certificate data	—	ICD-9	All deaths 1979-85	Not defined	—	—	E Depends on dementia being reported
Zhang et al	1990	Guam [72]	Guam, Mariana Islands, NW Pacific	Case register	Direct standardisation of incidence rates using 1960 Chamorro population age distribution	Neuropathological and clinical criteria[90]	All cases of Parkinsonism-Dementia complex	Not defined	Not stated	Not stated	C Completeness of case register may vary with time and location
Imaizumi	1992	[20]	Japan	Death certificate data	—	ICD-9	All AD deaths	≥35	Total population	931	E Relies on diagnosis being recorded
CSH&A Working Group Ebly et al Manfreda	1994 1994 1995	Canadian Study of Health & Aging[32, 33, 39]	Five Canadian provinces	Two-phase screening	3MS Clinical assessment (including all institutionalised individuals)	DSM-III	Random sample from community and institutionalised residents	≥65	10 263 (2 896)	1 125 (515)	B Robust design but ascertainment unclear; Ebly et al (1994) only included over-85s—in brackets[33]
Hébert et al	2000	Canadian Study of Health & Aging [34]	All ten Canadian provinces	Two-phase screening Incidence study (5 years)	3MS Clinical assessment (including all institutionalised individuals)	DSM-III (Vascular dementia)	Random sample from community and institutionalised residents	≥65	6 449	97	B Robust design but ascertainment unclear
White et al	1994	Epidemiologic Studies of the Elderly[59]	USA: East Boston, Iowa & New Haven	One-phase survey Incidence study (3 and 6 years)	Short Portable MSQ	SPMSQ ≥ 3 ICD-9	Community population	≥65	9 174	Not stated	E Methods unclear, comparability questionable

Table 4 continues on the next page.

Table 4 continued

Author	Year	Study	Setting	Methods	Measures	Diagnostic Criteria	Participants	Ages	Total N	Cases		Quality (A–E)
MRC CFAS Matthews et al Brayne et al	1998 2005 2006	MRC CFAS [31, 40, 41]	UK: Four urban and two rural areas	Two-phase screening Incidence study (2 years)	GMS AGECAT MMSE GMS assessment		Stratified random community sample	≥65	17 751 (prevalence) 7 175 (incidence)	630 incident	B	Robust design; unreported measures; two-fold variation in prevalence reasonable
Hendrie et al	1993	[48]	Canada: Two Cree reserves in Northern Manitoba and Winnipeg	Two-phase screening	Initial interview Clinical assessment (culturally adapted)	DSM-III-R	All registered Cree Winnipeg: age-stratified sample from Health Insurance database	≥65 (over-sampling of ≥80s in Winnipeg)	468	31	C	Comprehensive Cree register and reasonably comparable population, though institutional sample included; screening sensitive
Zhang et al Zhang et al	2005 2006	[46, 47]	Four regions of China	Two-phase screening	Chinese MMSE Clinical assessment Re-examination at 6 months	DSM-IV ICD-10	Stratified, multistage, cluster random sample from census	≥55	34 807	1 027	B	Thorough case-finding and 80-90% follow up; crude prevalences reported
Laditka et al Laditka et al Laditka et al	2008 2006 2006	[68-70]	South Carolina, USA	Case register	—	ICD-9-CM	AD cases	not defined	US Census	~33 754	B	Very robust methodology but unclear when spatial analysis conducted (i.e. birth, adulthood etc.)
Figueroa et al	2008	[60]	USA & Puerto Rico	Death certificate data	—	ICD-10	All AD deaths	not defined	Census	Not stated	E	Relies on diagnosis being recorded
Bermejo-Pareja et al	2008	Neurologic Disorders in Central Spain [19]	Spain: Las Margaritas, greater Madrid (working class), Lista, central Madrid (professional class) & Arévalo (agricultural)	Two-phase screening Incidence study (3 years)	Spanish MMSE Pfeffer activities questionnaire Clinical assessment	DSM-IV	Census data for geographically-defined areas	≥65	5 914 (prevalence) 3 891 (incidence)	306 prevalent 161 incident	A	Robust methodology
Steenland et al	2009	[29]	USA 1999-2004	Death certificate data	—	ICD-10	All AD deaths	not defined	1.7 billion	336 232	E	Relies on diagnosis being recorded
Gillum et al	2011	[65]	USA	Death certificate data	—	ICD-10	All AD deaths 1999-2000 and 2005-6	Not defined	Not stated	555 904 dementia 211 386 AD	E	Relies on diagnosis being recorded

Table 5. Studies meeting inclusion criteria: Town/city comparisons

Author	Year	Study	Setting	Methods	Measures	Diagnostic Criteria	Participants	Ages	Total N	Cases	Quality (A–E)	
Gurland et al	1979	US-UK Geriatric Community Study [28]	New York and London	One-phase survey	MSQ CARE interview (modified)	MSQ ≥ 8	Random sample of elderly in institutions	not defined	321	~117	C	Reasonable methodology; small study
Ichinowatari et al	1987	[53]	Japan: Sashiki village and Ikema Island, Okinawa	One-phase survey One year of follow up for confirmation	Not stated	ICD-9	Over-65s clinically diagnosed with dementia	≥65	919	45	A	Clinical assessment of entire populations
Copeland et al	1987	US-UK Cross-National (Diagnostic) Project [52]	New York and London	One-phase survey	GMS AGECAT	AGECAT DSM-III (London only)	New York: random cluster sample London: random sample from 3 000 GPs	≥65	841	—	C	Validity depends on AGECAT; DSM-III diagnosis confirms AGECAT diagnosis in London sample
Lobo Lobo et al	1990 1992	[55, 56]	Zaragoza, Spain and Liverpool, UK	One-phase survey	GMS AGECAT	AGECAT	Random age-stratified sample from census (Spain) or GP lists (UK)	≥65	2 620	134	D	Unclear if comparison is an a priori hypothesis; random sampling subverted in Spain
Hendrie et al Ogunniyi et al	1995 2000	Ibadan-Indianapolis Study [36, 42]	Ibadan, Nigerian and Indianapolis, USA	Two-phase screening	CSID Clinical assessment	DSM-IIIR and ICD-10	Community-dwelling Yoruba (total population survey of geographically-defined area) or African Americans living in the community (60% sample) or in 6 representative nursing homes	≥65	5 117	165	A	Robust, identical methodologies
Hendrie et al Ogunniyi et al	2001 2006	Ibadan-Indianapolis Study [35, 43]	Ibadan, Nigerian and Indianapolis, USA	Incidence study (2 and 5 years) Two-phase screening	CSID Clinical assessment	DSM-IIIR and ICD-10	Community-dwelling Yoruba or African Americans	≥65	4 606	187	A	Robust, identical methodologies
Artero et al	2003	3C Study [58]	France: Bordeaux (SW), Dijon (NE) & Montpellier (SE)	One-phase survey Incidence study (2 and 4 years)	Cognitive battery Clinical assessment (sample in Dijon)	DSM-IV	Random sample of non-institutionalised over-65s	≥65	9 693	~637	C	Reasonable methodology; in Dijon, screening estimated to be 87.5% sensitive and 78.8% specific

Table 6. Studies meeting inclusion criteria: Small area comparisons

Author	Year	Study	Setting	Methods	Measures	Diagnostic Criteria	Participants	Ages	Total N	Cases	Quality (A–E)	
Frecker	1991	[61]	Newfoundland, Canada	Death certificate data and case note scrutiny	—	not stated	All deaths mentioning dementia 1985-6	not defined	7 238	399	C	Relies on diagnosis being recorded or sufficient information in case notes; very robust otherwise including controls for sex and survival biases
Emard et al Perron et al Jean et al	1992 1993 1996	Projet IMAGE [66, 67, 71]	Saguenay-Lac-Saint-Jean territory, Québec, Canada	Case register	Reisberg GDS Screening Clinical assessment	Adapted NINCDS-ADRDA	AD cases	not defined	131 667 live births	235	C	Dependent on quality of case register; case ascertainment and representativeness of sample unclear; differential mortality a potential bias
Huss et al	2009	[62]	Switzerland	Death certificate data linked to census	—	ICD-10	Community-dwellers	≥30	4.65 million	45 716	D	Relies on diagnosis being recorded

Figure 1. PRISMA diagram showing selection of studies for inclusion in systematic review of geographical clustering of dementia prevalence and incidence

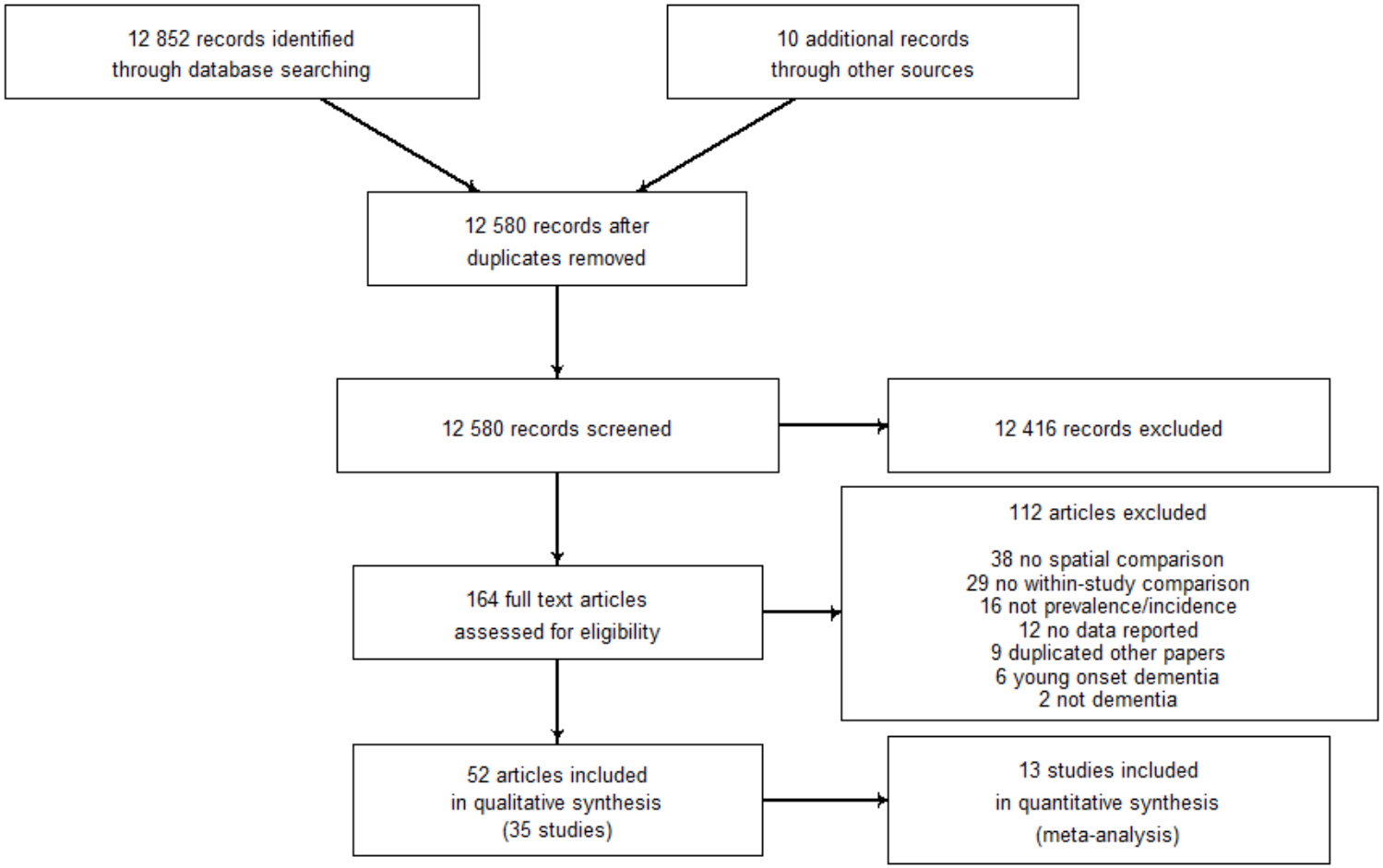
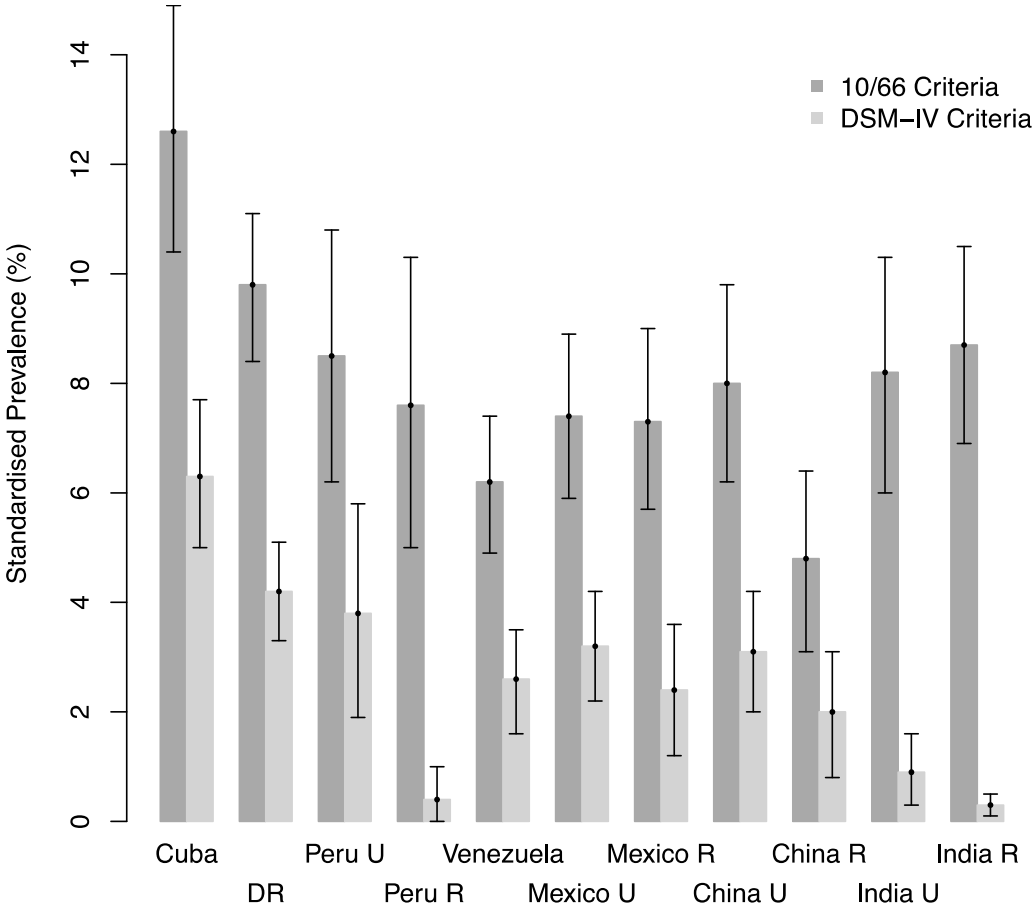
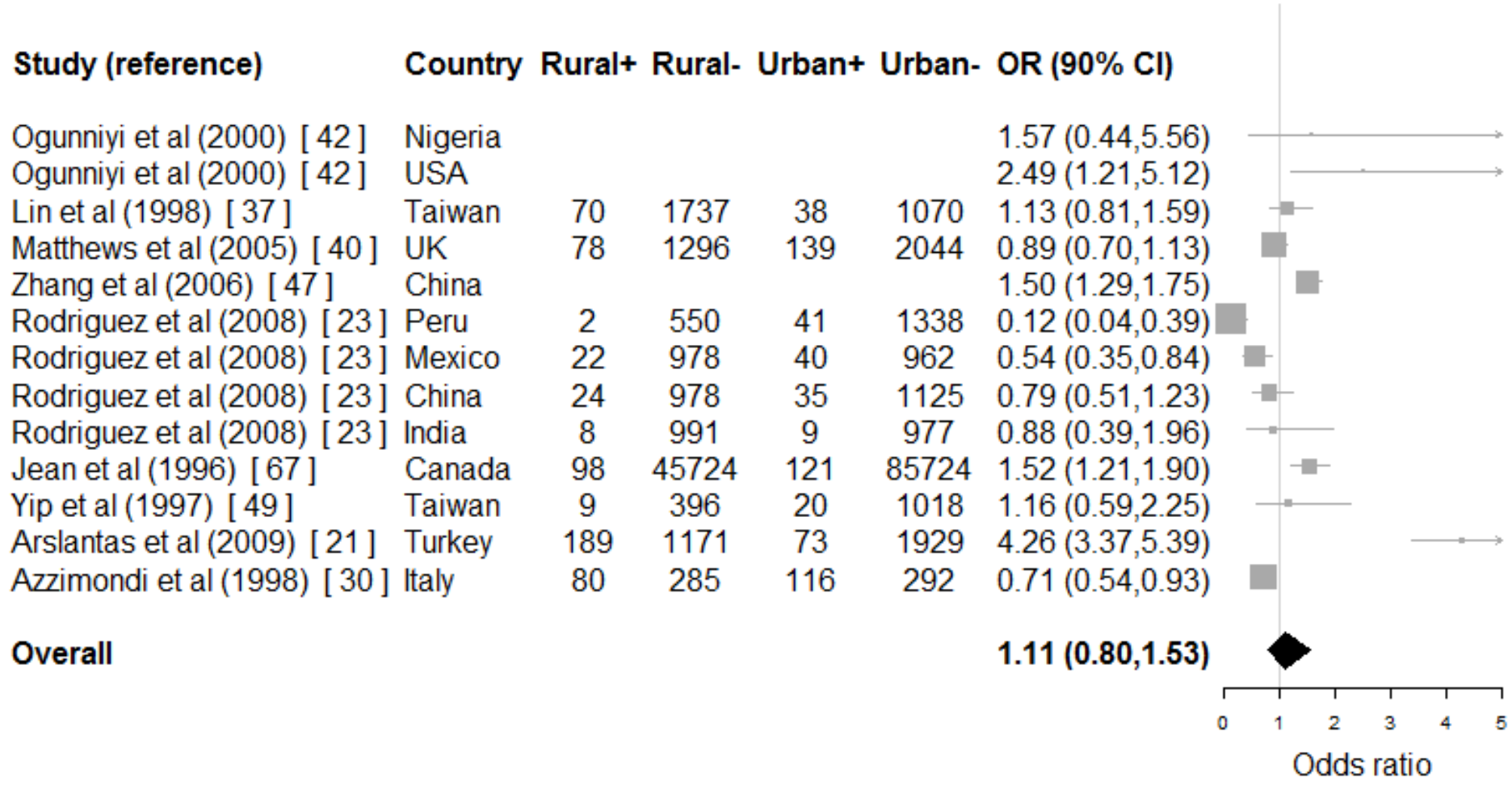


Figure 2. Comparison of standardised dementia prevalence (95% CI) with different diagnostic criteria. Constructed from 10/66 Dementia Research Group data.[23]



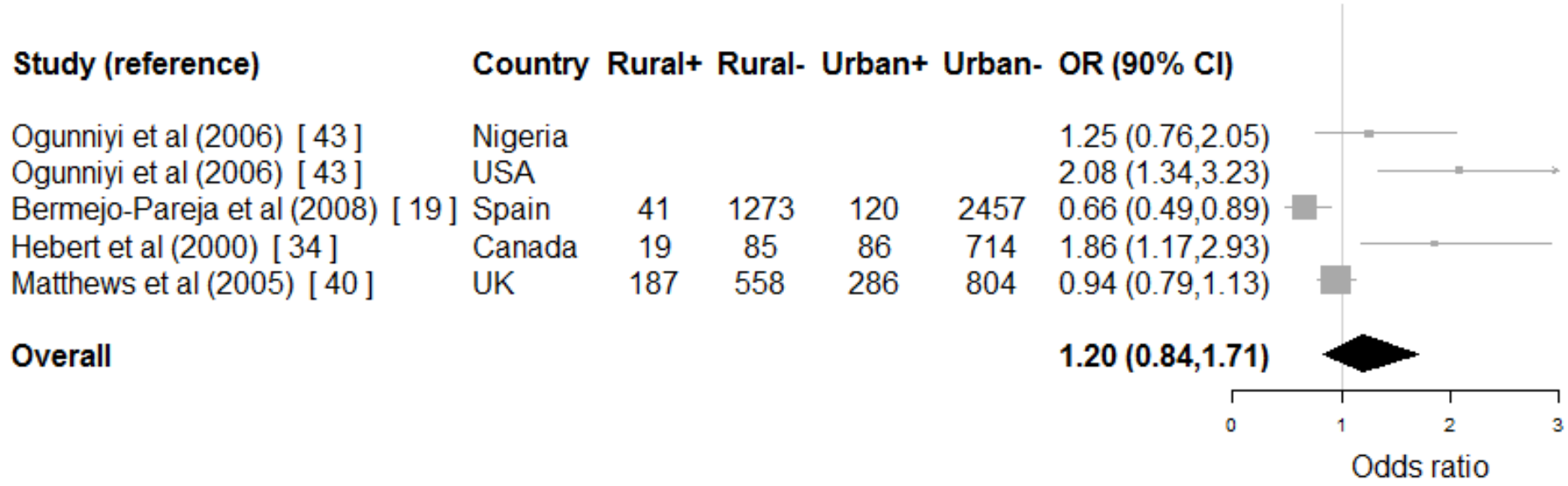
DR = Dominican Republic, U = Urban, R = Rural.

Figure 3. Meta-analysis with forest plot of urban/rural differences in dementia prevalence (Reference 23 using DSM-IV criteria).



Rural+: dementia cases in rural areas; Rural-: non-dementia cases in rural areas; Urban+: dementia cases in urban areas; Urban-: non-dementia cases in urban areas. Articles without case numbers reported odds ratios and 95% CIs rather than raw numbers. Urban areas form the referent.

Figure 4. Meta-analysis with forest plot of urban/rural differences in dementia incidence.



Rural+: dementia cases in rural areas; Rural-: non-dementia cases in rural areas; Urban+: dementia cases in urban areas; Urban-: non-dementia cases in urban areas. Articles without case numbers reported odds ratios and 95% CIs rather than raw numbers. Urban areas form the referent.